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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,779	04/20/2001	Amin I. Kassis	U0381-00001	2010

8933 7590 02/03/2003

DUANE MORRIS, LLP
ATTN: WILLIAM H. MURRAY
ONE LIBERTY PLACE
1650 MARKET STREET
PHILADELPHIA, PA 19103-7396

EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	4

DATE MAILED: 02/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,779	KASSIS ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Status of the Claims/Election/Restrictions

Applicant's election **without** traverse of Group I, claims 1-3 and 5-20 in Paper No. 5, filed 26 November 2002 is acknowledged.

Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5 (claim 4 is obvious in view of Shepard, *vide infra*).

Claim Objections

Claim 5 is objected to because of the following informalities: "manosidase" is a misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites decarboxylase (EC 4.1.1), glucokinase (EC 2.7.1) and hexokinase (EC 2.7.1) which are not hydrolases (EC 3.X) as required by claim 1, and accordingly, lack antecedent basis.

Claim 5 recites guanidinobenzodase which does not appear to be the art accepted name of any known enzyme. An EC for glutathionase could not be found, although there is glutathione thiolesterase (EC 3.1.2.7).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (c) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 5-15 and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hansen (US 5,851,527).

Hansen (US 5,851,527) disclose and claim (claims 1-5) a method of treating a tumor wherein an enzyme localized to the tumor converts a soluble prodrug (cytotoxic agent) to an insoluble drug which is deposited and accretes at the target tumor site. The enzyme itself is most preferably targeted by means of an antibody that recognizes the target site and the enzyme

wherein when the enzyme binds, its activity is not interfered. A number of prodrug-drug combinations are set forth throughout the disclosure. The prodrug or enzyme antibody conjugate may be labeled with various radiolabels (column 6, lines 28-60). Various boron addends and boron-dependent techniques can be used (column 11, line 4 to column 12, line 2). There is no limit on the enzyme hydrolase that may be used (column 5, lines 17-44) so long as it is not endogenous along the route of administration. The enzyme can be conjugated in situ or covalently in advance (column 5, line 45 to column 6, line 28). Many methods of administration can be used (column 14, lines 17-24+).

Claims 1, 5-15 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Griffiths et al. (US 6,361,774).

Griffiths et al. (US 6,361,774) disclose treating tumors with relatively serum insoluble cytotoxic drugs in prodrug more soluble conjugate form. Cleavage by targeted enzyme of the prodrug will deposit the less soluble drug at the target site (column 7, lines 11-23). The enzyme may be conjugated to a targeting antibody or a bispecific antibody that recognizes both enzyme and target may be used (column 2, line 64 to column 3, line 39 Many different enzymes may be used (column 6, lines 13-39). Many labels on the prodrug including radiolabels may be used (column 6, lines 40-50). Many methods of administration can be used (column 9, lines 55-61).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen (US 5,851,527) in view of Senter et al. (US 4,975,278), Shepard (US 6,495,553) and further in view of Camden (US 6265427), Griffin et al. (US 6156739) and Horwitz et al. (US 5,854,968).

The teachings of Hansen (US 5,851,527) have been discussed above. Hansen (US 5,851,527) lacks: alkaline phosphatase explicitly, using endogenous (overexpressed enzyme), or the specific radionuclides ^{211}At, ^{212}Bi and ^{213}Bi.

Senter et al. (US 4,975,278) disclose administering a prodrug of a tumor cytotoxic compound and subsequently an antibody-enzyme conjugate targeted to tumor cells that can convert the prodrug into active drug by hydrolysis (a process known as "ADEPT" – Antibody directed Enzyme Prodrug Therapy). A preferred hydrolase is alkaline phosphatase (instantly elected species). Also disclosed are penicillin V amidase and cytosine deaminase but could be any enzyme that can covert prodrug into drug (column 8, line 66 to column 9, line 39). Some suitable drugs that can be in the form of a prodrug are set forth at column 9, lines 40-58. For localization experiments, ^{125}I- and ^{131}I-labled drug were used (column 22).

Shepard (US 6,495,553) disclose that the prodrug activating enzyme may be 1) a nonendogenous enzyme delivered in an ADEPT process , 2) an endogenous, intracellular enzyme that is overexpressed in the target, 3) an enzyme which has been greatly enhanced in the target by loss of tumor suppressor function as result of prior chemotherapy, or 4) an expression product of a foreign gene in the cell - GDEPT (column 4 including Table 1).

Camden (US 6265427) disclose soluble prodrugs for tumor chemotherapy based on benzimidazole which can be converted to the active drug by enzyme hydrolysis.

Griffin et al. (US 6156739) disclose soluble prodrugs for tumor chemotherapy based on quinazolinone which can be converted to the active drug by enzyme hydrolysis.

Horwitz et al. (US 5,854,968) disclose that ^{211}At, ^{212}Bi and ^{213}Bi are known in the art as α-emitting radionuclides used in treatment of microscopic carcinomas and tumors.

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute the endogenous overexpressed enzymes as disclosed by Shepard (US 6,495,553) for the exogenous targeted enzymes in the process of Hansen (US 5,851,527) because

both of these disclosures are drawn to the same concept of treating tumors with target localized enzyme that convert prodrugs into active drug and Shepard clearly indicates that these are functionally equivalent enzymes that may be used in such a process. A person would be further motivated to use the specific radionuclides ^{211}At, ^{212}Bi and ^{213}Bi disclosed by Horwitz et al. (US 5,854,968) in the process of Hansen (US 5,851,527) because such radionuclides are disclosed to be used in radiotherapy of tumor and microcarcinomas. A person would be motivated to use alkaline phosphatase as the prodrug hydrolyzing enzyme because Senter et al. (US 4,975,278) disclose that this enzyme is suitable and preferred for use in an ADEPT process.

Camden (US 6265427) and Griffin et al. (US 6156739) are cited to establish that the specifically disclosed prodrug/drug pairs of the instant disclosure that allegedly precipitate in the tumors are known in the art for use in ADEPT methods for tumor therapy.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute endogenous overproduced enzymes of Shepard (US 6,495,553) for the exogenous targeted enzymes in the process of Hansen (US 5,851,527) so as to obtain precipitated chemotherapeutic drug, and further one that has specific tumor treating radionuclides bound and use alkaline phosphatase as the enzyme.

Firestone et al. (US 2002/0147138 A1) is cited but not relied upon to establish an analogous slow release of drug from prodrug *in situ* wherein the prodrug is only slowly cleaved to form the drug.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
January 30, 2003